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Fever in myocardial infarction: Is it still common, is it still predictive?

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Abstract

Background: *Before introduction of reperfusion therapy, fever was frequently observed in patients with acute myocardial infarction (AMI). Little is known about this symptom during the widespread use of primary percutaneous coronary intervention (pPCI). The aim of this study was to assess, whether body temperature is a predictor of impaired left ventricular systolic function in patients with AMI.*

Methods: *Our cohort included 171 patients (48 women) aged 57 (51–67) years, admitted due to the first AMI with ST elevation treated with successful pPCI. Standard body temperature measurements were performed twice a day. Left ventricular function was assessed by echocardiography using the wall motion score index (WMSI) and ejection fraction (EF). The following inflammatory response markers were determined on admission: C-reactive protein, fibrinogen and white blood cell count.*

Results: *Within 48 h of observation the median (1st; 3rd quartiles) peak body temperature was 37.0°C (36.7–37.2°C). A temperature above 37.5°C was observed only in 17 (10%) patients. There was no significant correlation between peak body temperature and any of the determined inflammatory response markers. WMSI was assessed at 1.3 (1.1–1.6), whereas EF at 56% (49–62%). There was no significant correlation between the left ventricular function and peak body temperature or determined markers of inflammation.*

Conclusions: *In the era of pPCI and aggressive antiplatelet treatment, fever is not a common symptom associated with uncomplicated AMI and thus not correlated with left ventricular function and markers of inflammation.* (Cardiol J 2012; 19, 4: 369–373)

Key words: myocardial infarction, fever, body temperature, inflammation

Introduction

Recent studies have established a pivotal role of inflammation in all stages of atherosclerosis — from plaque initiation to adverse complications of atherosclerosis, including myocardial infarction [1]. Fever remains the most common and the simplest noninvasive measure used in inflammatory diseases.

Fever can be defined as an elevation of the central thermoregulatory set point achieved by disinhibiting thermogenesis. Different pyrogenes (traditionally viral or bacterial) are recognized by Toll receptors in macrophages which lead to the release of interleukin-1β, tumor necrosis factor, and interleukin-6. These endogenous pyrogens stimulate the production of prostaglandin E2 which alters the set

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point of thermoregulation in the preoptic area of the hypothalamus [2].

Fever is one of the most frequent signs observed among hospitalized patients [3]. Its presence is connected with an increase in heart rate, cardiac work and oxygen consumption, which may be deleterious to myocardium affected by infarction. Animal models have shown that elevated body temperature (BT) was associated with larger infarct size and more common no-reflow phenomenon [4].

Previous data from 1970s' showed that the vast majority of patients with acute myocardial infarction (AMI) developed fever in the course of AMI. Another data revealed that early intervention with β-blockers may lower BT in the acute phase of AMI. Wide access to interventional therapy and aggressive pharmacological treatment may have changed this phenomenon and recent studies remain unclear. Thus, the aim of our study was to assess if fever is still common in the course of uncomplicated AMI and if it reflects the infarct size.

Methods

Study population

We investigated prospectively data of all consecutive patients hospitalized in our clinic with the diagnosis of STEMI treated with primary percutaneous coronary intervention (pPCI) within two years. Patients younger than 18 year-old, with the history of previous AMI, with known chronic or acute inflammatory disorder or admitted after 12 h from symptom onset were excluded from the analysis. None of the patients was treated with antibiotics within the first 48 h of hospitalization.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Study protocol

Standard axillary BT measurements were performed twice a day (at 6.00 am and 5.00 pm) during the period of hospitalization using mercury thermometers. Venous blood samples were drawn on admission to assay the following inflammatory response markers: C-reactive protein (CRP), fibrinogen (FBG) and white blood cell (WBC) count with peripheral blood smear. All patients within 90 min from admission had coronary angiography with subsequent primary PCI performed. Standard concomitant therapy (aspirin, thienopyridines, β-blockers, ACE-inhibitors, statins) was administered in all eligible patients. We also collected following data: age, sex, coronary artery disease (CAD) risk factors (cigarette smoking, hypertension, diabetes mellitus, hypercholesterolemia), heart rate, systolic blood pressure and signs of heart failure (according to Killip's classification) assessed on admission. All patients had echocardiography performed before discharge from hospital. Left ventricular (LV) function was assessed using the wall motion score index (WMSI) and ejection fraction (EF) by Simpson method.

Statistical analysis

Categorical variables were summarized as frequencies with percentage. Continuous variables were expressed as medians with interquartile range. The Shapiro-Wilk test was used to assess normal distribution of variables. Non-parametric statistics were used when variables had other than normal distribution. Correlations were assessed by using Spearman's rank correlation coefficient. Differences between continuous variables were compared by using the Mann-Whitney U test and Kruskal-Wallis analysis of variance. All statistical analyses were performed using STATISTICA 6.0 (StatSoft Inc., USA). A p-value < 0.05 was considered statistically significant.

Results

Our cohort consisted of 171 patients, aged 57 (51–67) years, 28% of them were women. Patients were admitted to our hospital within 3 (2–6) h of symptom onset. Eighty-seven percent of patients were in Killip class I. Coronary angiography revealed one-vessel disease in half of the group, in 47% of patients right coronary artery was the infarct-related artery. Primary PCI using bare metal stents in 9 out of 10 patients was successful (TIMI grade flow 3) in 94% of cases. During hospital stay, we found neither reinfarctions nor deaths in the investigated group. Other clinical features of the group and concomitant therapy are presented in Table 1.

Body temperature and inflammatory response markers

The temperature course within 48 h of observation is presented on Figure 1. The median peak BT was 37.0°C (36.7–37.2°C). We observed temperature above 37.5°C only in 17 (10%) patients (Fig. 2). WBC count on admission was 10.8 (8.6–12.9) $\times$ 10^3/$/mm^3$, neutrophiles were dominant in blood smear — 71.9% (62.8–79.9%). The median CRP level was 2.61 (1.48–5.35) mg/L whereas FBG was 3.7 (2.9–4.4) g/L. Killip class, age, sex, the presence of CAD risk factors, time from symptom onset and administered therapy didn't affect BT course. We found

Table 1. Patient (n = 171) characteristics, coronary angiography findings and concomitant treatment.

Age [years]	57 (51–67)
Women	48 (28%)
Heart rate [bpm]	75 (65–87)
Blood pressure [mm Hg]:	
Systolic	130 (120–140)
Diastolic	80 (70–90)
Anterior AMI	59 (35%)
Time from symptom onset [h]	3 (2–6)
Killip class:	
I	150 (87%)
II	17 (10%)
III	3 (2%)
IV	1 (1%)
Hypertension	117 (68%)
Diabetes	26 (15%)
Hyperlipidemia	78 (46%)
Family history of CAD	59 (35%)
Smoking status:	
None	42 (25%)
Current	94 (55%)
Serum creatinine [mg/dL]	0.9 (0.8–1.0)
Results of coronarography:	
One-vessel disease	91 (53%)
Two-vessel disease	55 (32%)
Three-vessel disease	24 (14%)
Infarct-related artery:	
LAD	60 (35%)
Cx	25 (15%)
RCA	81 (47%)
Stent	158 (92%)
TIMI grade flow 3	160 (94%)
Concomitant therapy:	
Aspirin	169 (99%)
Thienopyridines	161 (94%)
GP IIb/IIIa blocker	114 (66%)
Statins	170 (99%)
Beta-blockers	155 (91%)
ACE inhibitors	155 (91%)

ACE — angiotensin-converting enzyme; AMI — acute myocardial infarction; CAD — coronary artery disease; Cx — circumflex artery; GP — glycoprotein; LAD — left anterior descending artery; RCA — right coronary artery

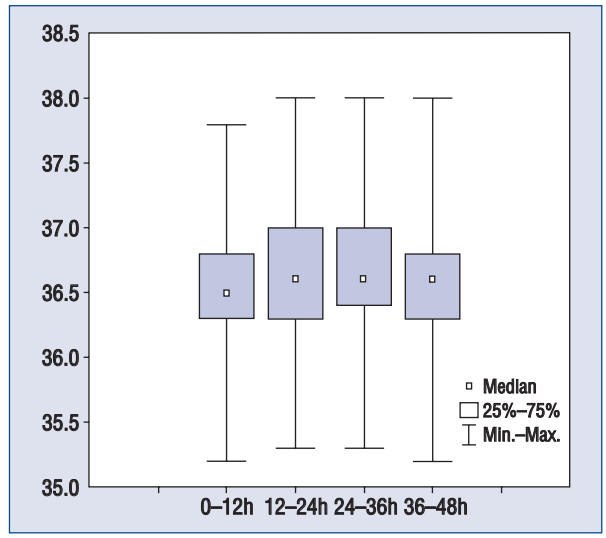

Figure 1. The temperature course within the first 48 h of hospitalization. Median, interquartile range, minimal and maximal values (°C).

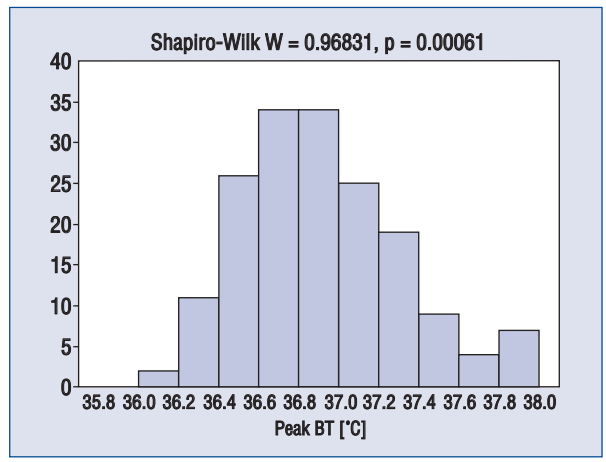

Figure 2. Distribution of peak body temperature (BT) within 48 h of hospitalization.

only weak correlation between peak BT and heart rate on admission (R = 0.22, p = 0.003). There was no significant correlation between peak BT and any of the determined inflammatory response markers.

Left ventricular function

Echocardiography was performed in most cases on the 3rd day of AMI. EF was assessed at 56% (49–62%) and WMSI at 1.3 (1.1–1.6). There was no significant correlation between LV function and peak BT (Figs. 3, 4) or the determined markers of inflammation. EF was statistically significant correlated with heart rate on admission (R = –0.20; p = 0.008) and Killip class (R = –0.15; p = 0.042), whereas WMSI with time from symptom onset (R = 0.21; p = 0.006), heart rate (R = 0.17; p = 0.030), Killip class (R = 0.17; p = 0.028) and systolic blood pressure measured on admission (R = –0.18; p = 0.016).

Discussion

In our well treated cohort we evaluated BT course in addition to markers of inflammation and

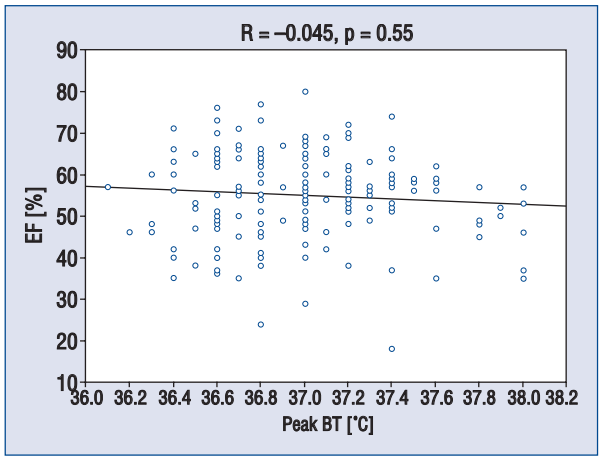

Figure 3. Correlation between peak body temperature (BT) and left ventricle ejection fraction (EF).

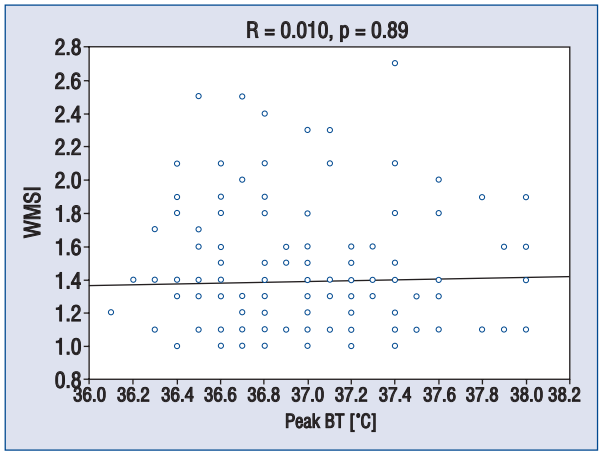

Figure 4. Correlation between peak body temperature (BT) and wall motion score index (WMSI).

its relation to LV function assessed by EF and wall motion score index. We found that only 10% of patients developed BT higher than 37.5°C. Regarding age, sex, risk factors and heart failure signs there was no difference in temperature course. Finally, peak BT was not correlated with EF, WMSI and inflammatory markers.

Lofmark et al. [5] in 1970s', studied data of 192 consecutive patients with AMI. BT, measured rectally, reached its maximum between day 2 and 5. Only 11% of patients did not develop fever during the myocardial course. BT rarely reached 38.2°C in the first morning and maximal temperature did not exceed 39°C during hospital stay. Prolonged fever duration (longer than 8 days) was connected with significantly higher SGOT concentrations.

Almost 10 years later, Risoe et al. [6] studied data of 65 patients admitted with AMI within 4 h of symptom onset. In this prospective study, 33 patients were randomized to timolol *iv* treatment and 32 to placebo group. BT was measured rectally twice a day. Temperature rose higher and the fever lasted longer in the placebo group (5.5 *vs* 4.5 days with BT > 37.5°C measured in the morning and 5 *vs* 4 days for BT > 37.7°C measured in the evening). Both the mean and the maximal temperatures were significantly lower in the timolol group. The maximal and mean temperatures were also significantly correlated with infarct size and ischemic area (assessed by cumulative creatine kinase [CK] release, QRS vector difference and initial ST vector magnitude) in the whole group and in the placebo group. The authors suggested that the fever response after MI is initiated by necrotic myocardium, and reduction of infarct size due to early β-blocker therapy may explain the reduction of the pyrexial response after AMI.

In another study, Ranjadayalan et al. [7] evaluated the effects of thrombolytic therapy on temperature responses in AMI. Eighty-five out of 156 patients received thrombolytic therapy, BT measurements were gathered through the first 72 h of hospitalization. Thrombolysis was associated with significant reductions in both mean (36.8 ± 0.6 *vs* 37.0 ± 0.6°C, $p < 0.001$) and peak temperature (37.6 ± 0.5 *vs* 37.9 ± 0.5°C, $p < 0.005$). Patients who did not develop Q-wave MI had lower mean and peak BT (36.7 ± 0.5 *vs* 36.9 ± 0.6°C, $p < 0.001$ and 37.5 ± 0.5 *vs* 37.8 ± 0.5°C, $p < 0.02$ respectively) than in the Q-wave infarction. BT were significantly correlated with peak CK release ($r = 0.31$ for mean and 0.25 for peak BT, $p < 0.005$). The authors concluded that the altered fever response after AMI is caused by reduction of infarct size.

BT was also evaluated in large clinical trials. Infarct size assessed by measuring CK-MB area under the curve and clinical outcomes were correlated with WBC count and initial BT in 1800 patients with STEMI treated with primary angioplasty — the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial (n = 960) or with fibrynolytics — the COMPlement inhibition in myocardial infarction treated with thromboLYtics (COMPLY) trial (n = 934). Increasing initial BT was associated with a longer time from symptom onset but not related to infarct size, heart failure and mortality. Patients with increased initial WBC count had greater infarct size and higher six-month mortality. Patients with increasing WBC count dur-

ing the first 24 h of observation had higher rates of shock, congestive heart failure, and death at 90 days. Baseline temperature and WBC count were not correlated with each other. The authors concluded that there was a direct association between inflammatory state and infarct size and adverse clinical outcomes. But the limitation of this study is lack of analysis of BT changes. Echocardiographic findings could be also useful [8].

Ben-Dor et al. [9] conducted an evaluation similar to our cohort of patients with STEMI. All 40 patients underwent urgent coronary angiography with subsequent successful PCI and optimal drug treatment. BT was measured rectally, which can explain slightly higher values of median temperatures — 37.4°C (36.9–37.6°C) *vs* 37.0°C (36.7––37.2°C) in our group. The median WMSI was 1.56 (1.23–1.88) which is slightly higher value in comparison to our results. They found significant correlation between peak BT and peak CK, WMSI (r = 0.41) and hs-CRP levels (assessed 24 h after admission, r = = 0.41), but not with WBC count. In multivariate analysis only CRP levels were independently related to LV function assessed by WMSI. Authors concluded that BT was related to infarct size, and unrelated to nonspecific inflammatory response.

Naito et al. [10] evaluated data of 156 patients with AMI treated with PCI (88%) and thrombolysis (12%) but with relatively low usage of statins (31%). Axillary BT was measured every 6 h for a week. Mean peak BT was 37.6 ± 0.6°C after 38 ± ± 22 h from symptom onset. Peak BT quartile was associated with significantly higher peak CRP level, but not with peak WBC count. EF assessed by echocardiography did not significantly correlate with peak BT, but ventriculography performed 2 weeks after AMI revealed significant association between peak BT and LVEF. Patients in the highest quartile of peak BT had more often heart failure, malignant ventricular arrhythmias, cardiac rupture or cardiac death during hospitalization. What is more, higher peak BT quartile was an independent determinant of readmission for heart failure. Authors suggested the existence of a relationship between systemic inflammatory response and postinfarction LV remodeling.

Limitations of the study

Relatively small group of patients with elevated BT is the most important limitation of this study. Axillary BT measurement may not be an accurate method — especially in critically ill patients. Repeated assays of inflammatory markers in addition to troponin levels could be useful as well.

Conclusions

In the era of pPCI and aggressive antiplatelet treatment, fever is not a common symptom associated with AMI and is not correlated with LV function and standard markers of inflammation.

Conflict of interest: none declared

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